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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/577,382	02/11/2008	**Shi Du Yan**	68548-PCT-US/JPW/JW	4714

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EXAMINER	
EMCH, GREGORY S	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/577,382	YAN ET AL.	
	Examiner	Art Unit	
	Gregory S. Emch	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22 and 27* is/are pending in the application.

4a) Of the above claim(s) *6-8 and 20-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,9-19 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Claims 1, 5, 15 and 19 have been amended, claims 25 and 26 have been cancelled, and new claim 27 has been added as requested in the amendment filed on 14 September 2009. Following the amendment, claims 1-22 and 27 are pending in the instant application.

Claims 6-8 and 20-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 06 January 2009.

Applicants' comments set forth on pp.1-2 of the Remarks filed on 14 September 2009 are acknowledged. Here, applicants assert that the cover page (i.e. PTO-326) of the 27 April 2009 office action lists claims 4 and 18 as being withdrawn from consideration but that the examiner has withdrawn the election of species requirement and has indicated that claims 1-5 and 9-19 are under examination (see 27 April 2009 office action at p.2). The examiner acknowledges that claims 4 and 18 are not withdrawn from consideration and that these claims have already been examined on the merits (see pp.3-10 of 27 April 2009 office action). The claim listing on form PTO-326 from the previous office action was obviously a mistake and has been corrected on the instant PTO-326.

Claims 1-5, 9-19 and 27 are under examination in the instant office action.

Information Disclosure Statement

As stated in the previous office action, the listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Withdrawn Rejections

The rejection of claims 1-4 and 9-18 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in response the amendment to independent claim 1 and 15 to recite "wherein the inhibitor of RAGE is selected from the group consisting of an antibody, an antisense molecule, an RNAi molecule, and a catalytic nucleic acid."

New and remaining issues are set forth below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5 and 9-19 stand rejected and claim 27 is newly rejected under 35 U.S.C. 103(a) as being unpatentable over Ganesh et al. (Hum Mol Genet. 2002, Citation U on PTO-892 dated 27 April 2009), in view of Yan et al. (Nature, 1996, Citation 5 on IDS dated 27 April 2006), further in view of Lado et al. (Epileptic Disord. 2002, Citation V on PTO-892 dated 27 April 2009).

The Ganesh reference teaches that advanced glycation endproducts (AGEs) are specifically associated with neurons in a mouse model of epilepsy, i.e. a mouse model of Lafora disease, which is characterized by seizures, cellular dysfunction, cell death

and eventual death (p.1251-1252, Abstract and Introduction). Ganesh teaches that the human disease and animal model are characterized by cytoplasmic inclusions (Lafora bodies) present in neurons, including those of the hippocampus and cerebral cortex, which also co-express the AGEs (p.1252, Results, paragraph 2). Ganesh teaches that the mouse model was characterized by extensive neuronal cell death in the hippocampus (p.1252, Results, paragraph 4) and explicitly states that the Lafora inclusions may induce neurotoxicity through interaction between AGEs and the receptor for advanced glycation endproducts (paragraph spanning pp.1259-1260).

Although the Ganesh reference strongly suggests that blocking the interaction between AGE and RAGE would be desirable for treating the neuronal damage in the cerebral cortex and hippocampus associated with this seizure disorder, the reference does not explicitly teach administration of an inhibitor of RAGE either during or soon after a seizure to reduce the extent of neuronal damage, as claimed. However, the Yan reference teaches that RAGE mediates the effects of the Aβ peptide on neurons and microglia and that there is increased expression of RAGE in damaged brain tissue in Alzheimer's disease, indicating that RAGE is relevant to the cell death in such damaged brain tissue (abstract). The Yan reference teaches experiments with RAGE and RAGE blocking antibody, which confirmed that RAGE specifically bound Aβ and mediated oxidant stress and neuronal damage, (which can be blocked by the antibody) (p.691, paragraph 2).

Although the Yan reference teaches that blocking the interaction between another ligand for RAGE (Aβ) and RAGE with an antibody that specifically inhibits

binding between RAGE and the ligand thereof would be desirable for treating the neuronal damage in Alzheimer's brain tissue, the reference does not explicitly teach administration of an inhibitor of RAGE either during or soon after a seizure to reduce the extent of neuronal damage, as claimed. However, the Lado reference teaches that neuronal damage in the hippocampus may occur immediately after the first seizure in a human patient and that early aggressive treatment of seizures is preferred (p.5, final paragraph).

Therefore, it would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention to arrive at the claimed invention by combining the disclosures of Ganesh et al., Yan et al., and Lado et al. Given Lado's teaching that treatment should occur immediately, it would have been obvious to the artisan of ordinary skill to treat with the antibody either during or soon after the seizure, as in claims 1, 9, 15 and 27. Further, Ganesh, Yan and Lado all teach data from diseases that occur in humans, as in claims 2 and 16. All of the references teach disorders that involve neuronal damage resulting from cellular dysfunction and cell death in the hippocampus and cerebral cortex, as in claims 3, 4, 17 and 18. As set forth above, Yan teaches an antibody that when contacted with RAGE specifically inhibits binding between RAGE and a ligand thereof, as in claims 5 and 19. None of the references explicitly teach administration within three days of the seizure, within one day, within six hours, within one hour or within 20 minutes of the seizure, as in claims 10-14, respectively. However, in the instant case the administration regime is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize (see

MPEP §2144.05). Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal administration regime given Lado's teaching that treatment should occur early after a seizure. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of administration regime would have been obvious at the time of applicants' invention.

As evidenced by Ganesh, the artisan of ordinary skill would have known that AGEs are associated with neuronal damage in the hippocampus and that inhibiting binding of AGE and RAGE to reduce the neuronal damage would be desirable for treating subjects with seizure disorders. As evidenced by Yan, the artisan of ordinary skill would have known that ligand-RAGE binding is implicated in the neuronal damage associated with Alzheimer's disease and that treatment of a subject with an antibody which inhibits ligand-RAGE binding would be effective in reducing neuronal damage. As evidenced by Lado, the artisan of ordinary skill would have known that hippocampal neuronal damage can occur immediately after the first seizure in a human and that early aggressive therapy for seizures in desirable. Given Ganesh's teaching that AGE/RAGE is implicated in neuronal damage/cell death in the hippocampus and given Yan's teaching that a RAGE blocking antibody would reduce neuronal damage in Alzheimer's disease, it would have been reasonable to predict that such antibody to RAGE could be successfully used to reduce the neuronal damage resulting from seizures, as claimed. Moreover, Yan's results with Alzheimer's disease related pathology supports a reasonable expectation of success. Further, the motivation to combine the references

flows logically from the disclosures of said references.

In the reply filed on 14 September 2009, applicants assert that Ganesh et al. disclose that in a mouse model for Lafora disease, advanced glycation endproducts are present in neuronal Lafora bodies but nowhere do Ganesh et al. disclose administering a RAGE inhibitor to reduce the extent of neuronal damage which would otherwise result from a seizure. Applicants assert that Ganesh et al. make no disclosure of any RAGE inhibitors. Applicants assert that Yan et al. disclose that amyloid-beta peptide is a RAGE ligand and further disclose that blocking this interaction with an anti-RAGE IgG or soluble RAGE inhibits binding between amyloid-beta peptide and RAGE but do not disclose or suggest administering a RAGE inhibitor to reduce the extent of neuronal damage which would otherwise result from a seizure. Applicants assert that Yan et al. do not disclose any antisense molecule, RNAi molecule, or catalytic nucleic acids which are RAGE inhibitors. Applicants assert that Lado et al. disclose that a first seizure may produce hippocampal injury and synaptic rearrangement and that some would favor early aggressive intervention to prevent the cycle of seizures from producing additional proconvulsant injury to the brain. Applicants assert that none of the cited references disclose or suggest that neuronal damage which would otherwise result from a seizure can actually be reduced by administering a RAGE inhibitor, as recited in applicants' amended claim 1. Applicants assert that the examiner states that all of the references teach disorders that involve neuronal damage resulting from cellular dysfunction and cell death in the hippocampus and cerebral cortex, but that the examiner has provided no evidence to show that a person skilled in the art would have a reasonable

expectation that compounds for treating amyloid-beta mediated neuronal damage in Alzheimer's disease may also be successful in treating neuronal damage which would otherwise result from a seizure.

Applicants' arguments have been fully considered and are not found persuasive. In response to applicants' arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicants' assertion that none of the cited references disclose or suggest that neuronal damage which would result from a seizure can actually be reduced by administering a RAGE inhibitor is not persuasive because the instant rejection is based on the combination of the references. Moreover, it is irrelevant whether Ganesh et al. make no disclosure of any RAGE inhibitors, since Yan et al. teach antibody to RAGE; an artisan of ordinary skill would immediately understand that such an antibody could be used to block RAGE-AGE interactions, as suggested by Ganesh. It is also irrelevant whether Yan et al. teach any antisense molecule, RNAi molecule, or catalytic nucleic acids which are RAGE inhibitors (i.e. the remaining non-elected inhibitors recited by the claimed Markush group), since Yan et al. teach said antibody.

Applicants are reminded that only a reason, suggestion or motivation need appear in the cited prior art in order to combine references under 35 U.S.C. 103. *Pro Mold Tool Col. v. Great Lakes Plastics, Inc.,* 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996). The collective teachings of Ganesh, Yan and Lado suggest that

the interaction between AGE ligands and RAGE is associated with neuronal damage in the cerebral cortex, including the hippocampus, and that blocking this interaction may be useful in reducing the neuronal damage, as claimed. Given that Ganesh teaches that neuronal cell death in the hippocampus results from activation of RAGE (paragraph spanning pp.1259-1260) and given that Yan indicates that RAGE is relevant to the cell death in Alzheimer's disease (see e.g. abstract), the artisan of ordinary skill would have had a reasonable expectation that an antibody inhibitor of RAGE would be useful in reducing neuronal damage associated with either seizures or Alzheimer's disease. Based on the disclosures of the prior art references of record, it would at least be obvious to try the claimed methods, which is proper to support a finding of obviousness under 35 U.S.C. 103(a). See the Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396) (available at <http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf>). If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense (see KSR International Co. v. Teleflex Inc. (KSR), 550 U.S. ____, 82 USPQ2d 1385 (2007). Therefore, the combination of the prior art references of record is deemed proper, and the instant rejection under 35 U.S.C. 103(a) is maintained.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached 9:00 am - 5:30 pm EST (M-F).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey J. Stucker can be reached at (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/G.E./

Gregory S. Emch
Patent Examiner
Art Unit 1649
02 January 2010

/Daniel E. Kolker/
Primary Examiner, Art Unit 1649
January 3, 2010